BRITISH CHILDHOOD CANCER SURVIVOR STUDY

RESEARCH PROTOCOL

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PURPOSE

GENERAL OBJECTIVES

At the core of the proposed research programme is the establishment of a population-based cohort of approximately 18000 patients who were diagnosed with childhood cancer between 1940 and 1991, in Britain, and who survived at least five years. The cohort would be ascertained using the population-based National Register of Childhood Tumours. There are two main general objectives:

    1)   To obtain estimates of the risks of particular adverse health outcomes occurring among survivors and their offspring and to investigate the variation of such risks in relation to different types of treatment received for childhood cancer.

    2)   To obtain family history information concerned with cancer, congenital abnormalities and hereditary conditions in survivors and their relatives to clarify the heritable component of childhood cancer and continue the search for cancer susceptibility genes.

The measures of adverse health outcomes and family history would be obtained by a postal questionnaire survey of survivors and their families. The questionnaire would initially be sent to the relevant general practitioner and they would decide whether it would be appropriate to send the questionnaire to the survivor (or a parent if the survivor is aged under 16 years). Measures of the treatment given for childhood cancer would be obtained from the co-ordinators of the clinical trials in which 30% of the cohort were treated. For the remaining 70% of the cohort we shall need to access the treatment details contained in the medical records of the original treating hospitals. The general objectives comprise a number of more specific objectives concerned with these patients who survived at least five years after diagnosis of childhood cancer.

SPECIFIC OBJECTIVES

    I   To investigate the risk of death from specific causes in relation to types of treatment for childhood cancer. In particular: to compare the observed mortality among survivors with that expected from the general population; to determine the long term risks of death from recurrent tumour and treatment related causes after different treatments.

    II   To determine the risks and causes of second primary cancers. Investigate the absolute risk of second cancer in relation to broad types of treatment using the cohort study. Study the causes of second cancers using nested case-control studies. The maximal period of follow-up obtained by contacting survivors directly would provide a basis for the most powerful and informative analyses possible, particularly in relation to modern treatment protocols. The proposed study would extend the period of follow-up for the ascertainment of second primary cancers by a decade beyond that accumulated at present. Future case-control studies of second cancers could include information from biological material indicating whether there is evidence of specific germ line or somatic mutations in known cancer susceptibility genes. For example TP53, ATM, NF1, NF2, BRCA1, BRCA2 etc. This would complement the usual detailed cytotoxic drug and radiation dosimetry measures which have been the only factors analysed in previous case-control studies. However, such biological studies would be the subject of separate grant applications and ethical approvals.

III   To determine the risk of cardiac, pulmonary, renal, hepatic, intestinal and other major organ toxicity in relation to types of treatment received for childhood cancer.

IV   To investigate the fertility of survivors in relation to cytotoxic drugs and radiotherapy received. In particular, explore the risk of gonadal failure, and age at gonadal failure, in relation to aspects of treatment for childhood cancer.

V   To further evaluate the risk of adverse outcomes of pregnancy (recognised spontaneous abortion, stillbirth, low birthweight and congenital abnormalities) in relation to types of treatment for childhood cancer.

VI   To monitor the health of the cohort of offspring of survivors. In particular, compare the observed numbers of specific types of cancer and deaths from particular causes among offspring with the corresponding numbers expected from the general population.

VII   To further clarify familial aggregations of cancers involving childhood cancer. Establish estimates of risk to family members for use in counselling, surveillance and interventions strategies with the objective of prevention. In particular, compare the observed frequency of cancer among first degree relatives of survivors with that expected from the general population. Identify families in whom the role of both known and as yet unidentified cancer susceptibility genes may be investigated using molecular genetic techniques.

VIII   To ascertain the extent of use made of health services by survivors including frequencies of consultation with general practitioners and hospital doctors, and compare these with frequencies expected from the general population. Determine the amount of drugs and medications which survivors have been prescribed by medical doctors.

IX   To compare:

- the frequency of smoking, and quantity smoked, among survivors with the frequency expected from the general population.

- the education attainments of survivors with those expected from the general population.

- the self assessed health related quality of life among survivors with that expected from the general population using the SF36 questionnaire.

Only crude measures of exposure to treatment would be obtained for the generality of the cohort. For those treated with chemotherapy individual drugs received, but not doses, would be recorded. For those treated with radiotherapy a qualitative indication would be recorded of whether the volume of tissue directly irradiated included an organ of particular interest (for example the gonad, uterus, heart or lung) or whether the organ was on the edge or outside of the volume of tissue directly irradiated. If there is evidence that the risk of a particular adverse outcome is increased following specific types of treatment then a nested case-control study could be executed to investigate the question of aetiology in a more rigorous way. Such case-control studies would involve the determination of the cumulative doses of individual cytotoxic drugs, doses of radiation received within the relevant body organs and measures of important potential confounders - for example smoking history and genetic conditions diagnosed in the survivor which are known to predispose to the specific adverse outcome concerned. Finally, investigate the possibilities of obtaining biological material from survivors for evidence of mutations in genes known to predispose to the specific adverse outcome concerned. It is important to note that most such nested case-control studies and all such biological studies would be the subject of separate grant applications and ethical approvals - see EXTENT OF RESEARCH PROTOCOL below.

NEW AND SIGNIFICANT INFORMATION EXPECTED FROM THE PROPOSED STUDY

Almost all previously published studies of late effects of treatment for childhood cancer have been based on the experience of a single or a small number of treatment centres, occasionally they have been based on the follow-up of participants of a clinical trial, almost never have such studies been population-based. There is a study progressing in the USA which is based on 27 major treatment centres - this is described below. There are profound limitations affecting the interpretation of results from studies which are not large and population-based. From the start, treatment centre based studies and clinical trials are likely to be referred an unrepresentative group of patients with any particular cancer. However, the serious potential for bias increases as the former paediatric patients become adults. A variety of influences inevitably mean that a substantial proportion will become lost to follow-up. It is often suggested that the survivors who experience health problems are more likely to keep in contact with the treatment centre than those survivors who remain healthy. The only late effect for which there has been sufficient published to investigate this potential for bias is second cancer. We have reported elsewhere that the absolute risks of second primary cancers from large population-based cohorts of childhood cancer survivors are consistently substantially less than those from large treatment centre based studies. [1] A substantial element of this discrepancy is likely to be bias. [1] A recent paper which caused considerable concern reported, on the basis of a treatment centre based study, that 35% of girls irradiated for Hodgkin's disease developed breast cancer by age 40 years. [2] An accompanying editorial commented on the potential for bias, as a substantial fraction of the cohort were eventually lost to follow-up. [3] The results of such treatment centre based studies need to be interpreted with great caution until confirmed by appropriate population-based cohort studies. The only large population-based study so far published relating to this issue involved 1641 survivors of Hodgkin's disease diagnosed in children or adolescence in the Nordic Countries. [4] At 30 years from a median diagnosis age of 16 years, that is at about age 46 years, the cumulative risk of breast cancer was 12%, substantially less than the treatment centre based study cited above. [4]

Almost none of the adverse health outcomes addressed in our study objectives have been previously investigated using a large population-based cohort which can guarantee almost complete follow-up. By taking advantage of the unique facilities available through the National Health Service Central Registers such a study is possible in Britain. [5]

The proposed study would provide, for the first time, reliable and unbiased risk estimates of a comprehensive spectrum of adverse health outcomes which may be increased as a result of childhood cancer or its treatment. Such information is of considerable importance to survivors of childhood cancer, their families and to the clinicians who counsel such families. Survivors who were treated in the past are likely to benefit from the proposed study as a result of information gained enabling the targeting of surveillance with a view to early diagnosis and intervention. Patients who are treated in the future are likely to benefit from the proposed study as it will provide the most complete and accurate insight available of the long-term adverse consequences of different treatments. Such information when taken together with the corresponding survival prospects associated with different treatments should help design future protocols to achieve an appropriate balance between the long-term benefits and risks. Alternatively the information will enable a clinician to discuss with the patient and family both the advantages and disadvantages of different treatment strategies in the long-term, and so enable the patient and family to participate in decision making in an informed way.

An advantage of including a wide range of years of diagnosis, 1940 to 1991, ensures that the proposed cohort study may satisfactorily address **both the long-term risks associated with therapy (a third of the survivors will be aged over 30 years old) and the consequences of modern multi-agent chemotherapy based protocols (a half of the survivors will have been treated since 1980) - see Appendix A.** The older survivors will be particularly informative concerning the long-term effects of radiotherapy in causing second cancers, major organ toxicity and adversely affecting the outcome of pregnancies and health of offspring.

The establishment of the proposed large population-based cohort study would provide an important opportunity to investigate the involvement of genetic susceptibility in development of adverse outcomes. For the future it is critical to develop understanding of the possible interactions between genotype and different elements of therapy with a view to modifying therapy to suit an individual's genotype. During the period of the proposed programme of research we would initially seek separate funding to study the involvement of genetic susceptibility (including mutations in cancer susceptibility genes) in the development of multiple primary neoplasms.

As most previous studies were treatment centre based, the patients with a particular cancer would have been treated in a standardised way. The proposed study has another advantage over these previous studies because it will include survivors of each specific cancer who have been treated in every way used in practice throughout Britain. Consequently, there will be much greater heterogeneity in the treatment received for each specific cancer. This will greatly help identify elements of therapy with an increased risk of an adverse outcome.

Soon one in a thousand of the general population will be a survivor of childhood cancer. The demand which this survivor population will put on the resources of the National Health Service is largely unquantified. The Pilot Study questionnaire asked survivors the amount of different medications they had been prescribed by doctors. We also asked about the frequency of contact with general practitioners and hospitals, using questions from the General Household Survey. This will enable comparison of the observed frequency of use primary and secondary health care facilities with that expected from the general population.

Survivors of childhood cancer are known to be at an increased risk of second cancers both because of the carcinogenic effects of anti-cancer therapy and as result of constitutional genetic susceptibility. In addition, some survivors may have an impaired immune system as a result of anti-cancer therapy. Therefore survivors may be at a greater risk of carcinogenic effects of smoking than are other members of the general population. Again, using questions taken from the General Household Survey, the Pilot Study questionnaire asked survivors about smoking habits. Thus enabling comparison of the tobacco consumption of survivors with that of the general population. Such information is critical in the planning of possible intervention strategies to reduce smoking among survivors.

FURTHER JUSTIFICATION FOR THE PROPOSED STUDY

There is a study currently being executed in the USA which is based on 27 major treatment centres and involves sending a postal questionnaire to 22,000 individuals, or a close relative of these individuals, who were treated for cancer before age 21 years, between 1970 and 1986, and who survived at least five years. The questionnaire is concerned with adverse health outcomes which may be related to treatment and familial aggregation of cancer and is broadly similar in content to that proposed for Britain.

Would it be possible to use information from this study and assume that it applies to Britain?

Such an approach would be untenable for adverse outcomes of health which may be related to treatment. This is as a consequence of two substantial differences. Firstly, the types and patterns of development of treatment over recent decades have been different in the USA and Britain. Secondly as was confirmed above in the context of second cancers, as a result of referral bias at diagnosis and substantial losses to follow-up, treatment centre based studies are susceptible to considerable bias. In addition, studies of the familial aggregations of cancer could also be biased when based on treatment-centre based studies. For example major centres are likely to be preferentially referred patients presenting with complex and difficult disease and this may be related to familial risk. The proportion of older survivors will be substantially less in the US investigation and so their ability to study the long-term effects of therapy will be extremely limited when compared with the proposed British study.

BACKGROUND

THE NEED FOR LONG-TERM FOLLOW-UP

Only 26% of children diagnosed with cancer in Britain during the period 1962-70 survived at least 5 years from diagnosis, whereas the corresponding percentages for children diagnosed during 1971-85 and 1986 -88 were 50% and 65% respectively. This outstanding improvement in survival was mainly attributable to the introduction of chemotherapy. As survival has greatly improved, the need to assess the quality of survival has increased correspondingly. It has become essential to know the risks of long-term complications of childhood cancer and its treatment, and to understand the extent to which specific elements of therapy and biological characteristics of survivors (particularly genetic factors) are involved in the development of such complications.

LONG-TERM SURVIVAL, CAUSES OF DEATH AND CURE

The most serious adverse health outcomes of childhood cancer or its treatment result in death. We have previously executed three national studies investigating long-term survival, causes of death and cure after childhood cancer in Britain; each of these study populations were ascertained using the population-based National Register of Childhood Tumours. [6, 7, 8]

In the past almost all studies of survival following childhood cancer have tended to concentrate on the proportion of patients surviving to 5 years from diagnosis, with little consideration given to what happens subsequent to 5 years' survival. With most patients surviving beyond this point, two important clinical concerns needed to be addressed. Firstly, had the modern treatments which greatly improved survival to 5 years truly cured most children or merely postponed death from recurrent tumour? Secondly, whilst many modern anti-cancer therapies were known to have toxic 'side-effects', in the short-term, almost nothing was known concerning the risks of fatal toxic effects of treatment in the long term. A recent large population-based study in Britain, which was primarily established to investigate these two concerns, has provided reassurance in relation to both. [8] The study compared long term survival of 9000 5 year survivors diagnosed during 1971-85 and 4000 5 year survivors diagnosed during 1940-70. The early 1970s was the period when chemotherapy was widely introduced into the treatment of childhood cancer in Britain. The risk of dying of recurrent tumour, in the 10 years subsequent to 5 year survival, fell from 12% among those diagnosed during 1940-70 to 8% among those diagnosed 1971-85; the corresponding risks of dying of a treatment-related death rose only slightly from 1% to 2%. [8] Therefore modern therapies, involving the widespread use of chemotherapy, have resulted in cure for a greater proportion of 5 year survivors than was possible before introduction of such therapies. The extra risks associated with these benefits, in terms of increased treatment-related mortality, are comparatively small.

Although our previous studies were reassuring in terms of both efficacy and the toxicity of treatments given until 1985, further information is required for two main reasons. Firstly, the follow-up after modern therapies in previous studies was limited, and it is of critical importance to establish any changes in the risk of death from specific treatment-related causes as the survivor population ages. For example, the risk of cardiac deaths among those who received cardio-toxic therapy in childhood as they enter middle age. Secondly, therapies are constantly changing and it is important to study the risk of specific causes of death subsequent to therapy introduced since 1985.

RISKS AND CAUSES OF SECOND PRIMARY CANCERS

Second cancer is arguably the most devastating complication to develop in someone already apparently cured of cancer. It has been known for many years that survivors of childhood cancer are at an increased risk of developing another cancer in comparison with that expected from general population rates of cancer. It is, therefore, important to obtain unbiased and reliable estimates of the risk of occurrence of different types of second cancer; also to identify elements of therapy and genetic constitution which are associated with the increased risk.

In Britain, the existence of national registries enables the study of second cancer among all children diagnosed with cancer. Such large population-based series of survivors have two important advantages: firstly, being population-based ensures selection factors which bias treatment-centre based series are avoided; secondly, as a result of including large numbers of survivors reliable estimates of risk are obtained.

We have already investigated the risks and causes of second cancers after childhood cancer in Britain in a number of studies. [9, 10, 11, 12, 13, 14, 15, 16, 17] In collaboration with other investigators we have also examined the long-term risks of cancer following irradiation in childhood; these studies included the data from the children irradiated in Hiroshima and Nagasaki during the Second World War. [18, 19, 20, 21,22] We have also collaborated with other European investigators to study the risks and causes of second cancer after childhood cancer in Western Europe generally. [23, 24]

Our most detailed national studies carried out so far relate to second primary leukaemia, [16] and second primary bone cancer. [17] These studies have identified the elements of treatment for childhood cancer which are associated with each type of second cancer. The absolute risks and dose-response relationships which we produced have provided a sound basis for: counselling survivors and their families; targeting surveillance on groups of survivors at substantially increased risk with a view to early diagnosis and intervention; planning future treatment protocols to achieve an appropriate balance between the risks and benefits of different treatment strategies.

We are just completing a detailed study of the risks and causes of carcinoma after childhood cancer. We plan two further detailed studies of second cancers after childhood cancer - one of second CNS tumours the other concerning second soft tissue sarcomas. In all such future studies we plan to obtain blocks of tissue stored in the pathology departments which originally diagnosed the cancer for diagnostic review and to provide a source of DNA for separately funded molecular genetic studies.

CARDIAC DYSFUNCTION

After chemotherapy

It has been known for about two decades that there is an increased risk of acute cardiac toxicity following cumulative doses of anthracyclines which exceed $500mg/m^2$. However, only recently have the longer term cardiotoxicity effects of anthracycline therapy begun to be identified; particularly among children exposed to cumulative doses less than $500mg/m^2$. In 1991, two studies were published which aroused particular concern.

In one study from the Memorial Sloan-Kettering Cancer Center, 47 of 201 children (23%) who had received cumulative doses of between 200-1275mg/m^2 (median 450mg/m^2) had abnormal cardiac function as assessed by echocardiogram testing at 4-20 years (median 7 years) after completion of anthracycline treatment. [25] The increased risk of cardiac abnormalities was associated with the cumulative dose of anthracyclines, length of follow-up and mediastinal irradiation.

The other study was of 115 children treated for ALL who were evaluated (using 24 h electrocardiogram, exercise testing and echocardiography) 1-15 years from treatment involving doxorubicin. [26] Three (17%) of the 18 patients who received a cumulative dose of 45mg/m^2 had mild but detectable cardiac abnormalities. In contrast, 65% of patients who had received 228-550mg/m^2 (median 360 mg/m^2) revealed evidence of cardiac abnormalities. [26] In a further study, these investigators included additional patients with osteosarcoma who had been treated with doxorubicin.[27] They examined echocardiograms from 120 children and adults who had received cumulative doses 244-550mg/m^2 of doxorubicin a mean interval of 8.1 years previously.[27] A group of 296 normal subjects provided control data. All echocardiographic parameters measured were on average statistically abnormal among the survivors of malignant disease a minimum of 2 years after the end of therapy, with more frequent and severe abnormalities in female patients. It was concluded that female sex and higher rates of administration of doxorubicin were independent risk factors for cardiac abnormalities, and that the prevalence and severity of abnormalities increased with longer follow-up. [27]

Nevertheless, at present, the relation between the measures of cardiac abnormality identified by screening patients during and after therapy and the long term risk of serious cardiac disease is very uncertain. This is a priority area for further research and it is essential to monitor all survivors treated with anthracyclines.

Cyclophosphamide in high doses is associated with acute cardiac problems, most studies involved high dose preparatory regimens for bone marrow transplant. The possible long term effects of lower doses are uncertain.

After radiotherapy

The cardiotoxic effects of radiotherapy in childhood and adolescents have been clearly demonstrated among survivors of Hodgkin's disease. A cohort of 635 patients treated for Hodgkin's disease before 21 years of age at Stanford University between 1961-1991, and followed up for an average interval of 10.3 years, yielded 12 deaths from cardiac disease. [28] This was 30 times the number of such deaths expected from the death rates of general population of the US. Acute myocardial infarction accounted for 7 deaths which corresponded to 42 times the number expected. Six of these 7 deaths occurred after treatment not involving chemotherapy. These authors concluded that mediastinal irradiation of 40-45 Gy increases the risk of death from coronary artery and other cardiac disease, and that the risk increases within 5 years of irradiation. The long-term follow-up of all survivors treated with thoracic irradiation is clearly essential.

PULMONARY, RENAL, HEPATIC, INTESTINAL AND OTHER MAJOR ORGAN DYSFUNCTION - EXCLUDING REPRODUCTIVE ORGANS

The evidence for a relation between treatment for childhood cancer and adverse effects on other major organ systems were summarised by us in a recent review. [1] This may be consulted if a detailed description is required. Recently a monograph appeared concerned exclusively with the effects of childhood cancer and its treatment on survivors. [29] However, despite this literature, knowledge of the long-term consequences of therapy on almost all major organ systems is extremely limited, and does not exist for the effects of modern chemotherapy.

FERTILITY

There have been few large epidemiological studies of fertility after childhood cancer. The most informative such study was carried out in relation to 2283 long term survivors of childhood and adolescent cancer diagnosed during the period 1945-75 in five cancer centres in the US. [30] Patients were diagnosed before age 20 years, survived at least 5 years and attained the age of 21. The control population consisted of 3270 siblings. An interviewer administered questionnaire was used to collect information; the response rate was 91%. Survivors were 15% less likely than siblings to have ever begun a pregnancy. Both male and female survivors who had previously received abdominal irradiation were 25% less fertile than siblings. Male survivors who had received alkylating agent therapy were 60% less fertile than siblings, irrespective of whether they also received abdominal irradiation. Females who had received only alkylating agent therapy experienced no appreciable effect on fertility

A further study of premature menopause in this same study population has also been reported. [31] This study was restricted to 1067 female survivors who were still menstruating at age 21. Menopause status in survivors was compared with that in 1599 female siblings. Women diagnosed before age 13 were not found to be at greater risk of menopause than their siblings. Women who had been diagnosed between 13 and 19 years, had 4 times the risk of menopause experienced by siblings during ages 21 to 25 years, the discrepancy diminished at older ages. Among survivors diagnosed between age 13 and 19 years, the risk of menopause during their early 20s was 4 and 9 times higher than in siblings after radiotherapy alone and alkylating agents alone, respectively. At ages 21 to 25 years, among woman treated with abdominal irradiation and alkylating agents, the risk of menopause was 27 times that in siblings. By age 31 years, 42% of survivors had experienced menopause compared with 5% of siblings. The authors commented on the clinical implications and concluded that treatment for cancer during adolescence is associated with a considerable risk of premature menopause among women menstruating at age 21 years.

The only British data which give some insight into fertility are concerned with the observed and expected numbers of live births to female survivors of childhood cancer treated in Britain and born before 1963.[32] The expected live births were derived from general population age specific fertility tables for different calendar years. Only 57% of the expected live births were observed. The deficit was greatest among the young, in that, among those aged below 20, 20-24, 25-29 and 30-34 years old the percentage of expected live births actually observed was 51%, 58%, 57% and 64%, respectively.

With increasing use of more gonadal toxic therapy in more recent years than for patients included in the studies referred to above, there is a clear need for further large and population-based epidemiological studies to quantify the risks. With the tendency for women in general to delay childbearing, information is needed to advise women of the shorter periods during which they are likely to be fertile following treatment for childhood cancer.

PREGNANCY OUTCOME AND HEALTH OF OFFSPRING

All previous large scale epidemiological studies of pregnancy outcome among survivors of childhood cancer have included almost no survivors treated in the last 20 years. During this period chemotherapy regimens have become more aggressive both in terms of the number of drugs and the doses used. There is a considerable gap in our knowledge relating to the possible effects of these modern treatment regimens on the germ cells of survivors of both sexes and the other reproductive organs of female survivors.

Survivors of cancer occurring in childhood or early adult life form one of the largest groups of people exposed to high doses of mutagenic agents before reproducing. Radiation dosimetry and cytotoxic drug doses are obtainable from detailed clinical records (although the retention of such records in the future is under threat in Britain). [33] Assessment of a possible relation between treatments for cancer and adverse reproductive outcomes is important to families and clinicians–but it also provides valuable data on possible associations between exposure to mutagens and germ cell mutagenesis in the wider community.

In a recent review it was noted that only three large cohort studies of offspring of survivors of childhood cancer have been published, but together these account for nearly 4000 offspring. [34] In the more numerous small (<200 offspring) cohort studies, no malignant neoplasm has been observed in the offspring. [34] Cancers were diagnosed in offspring within each of three large cohorts. However, when inherited retinoblastomas and a family with Sipple's syndrome were excluded there were only seven cases. About five cancers would have been expected by chance. Only one of the seven survivors to whom these children were born had received treatment that might have been mutagenic to germ cells. Some of the seven parent/offspring pairs of malignant neoplasms seemed consistent with the Li-Fraumeni familial cancer syndrome. [34] Even the relatively large numbers of offspring available from these three cohorts do not provide data from which an increase in the risk of the generality of childhood cancers could be detected with confidence.

Serious congenital malformations, another indicator of a possible germ cell mutagenic effect of treatment, are important because they occur more commonly than malignant neoplasms in young children–so fewer offspring and a shorter follow up will achieve a study of comparable statistical power. The large studies reported so far have found no evidence of an increased risk of congenital malformations associated with cancer treatment that was potentially mutagenic to germs cells. [34] Again, however, larger numbers would be needed to rule out an association. [34]

The most extensive data on the effects of irradiation on germ cells come from survivors of the atomic bombing of Hiroshima and Nagasaki. These studies found no evidence that increased exposure to gonadal irradiation was associated with either an increased risk of pregnancies ending in still birth, or an increased risk of neonatal mortality, congenital malformations, or cancers in the offspring. [34]

Radiotherapy to the abdomen of girls increases the risk of subsequent pregnancies ending in miscarriage, and their offspring are at an increased risk of having a low birth weight and of perinatal death. [34] The underlying mechanism is uncertain, but it seems unlikely to be due to germ cell mutagenesis. The more likely explanations are an impaired vascular supply affecting placentation and inelasticity of the uterus due to radiation fibrosis. [34] A long term increased risk of serious cardiac disease is suspected among patients treated with anthracyclines. [34] Concerns have been expressed regarding a possible increased risk of cardiac problems during pregnancy after such treatments, but no satisfactory data are available to address this question.

Apart from the small groups of survivors identified above, most pregnancies and offspring of survivors do not seem to be at an increased risk of adverse outcomes. Vigilance should be maintained, in particular to identify any newly introduced elements of treatment that may have unforeseen long term adverse effects.

FAMILIAL AGGREGATIONS OF CANCER AND MOLECULAR GENETIC STUDIES

Epidemiological evidence concerning the genetic origins of childhood cancer has historically been obtained from the study of cancers in the blood relatives of affected patients, from studying patients developing multiple primary cancers and from investigating the occurrence of genetic conditions and congenital abnormalities which are associated with the occurrence of cancer. Therefore the questionnaire for the Pilot Study contained a section which obtained information relating to the occurrence of cancer, genetic conditions and congenital abnormalities in the survivors and their first degree relatives.

We have previously studied the patterns of risk of cancer in families with hereditary retinoblastoma and provided risk estimates appropriate for genetic counselling. [35] Through the study of the occurrence of cancer in the offspring of Wilms' tumour survivors we identified three of 146 offspring produced who developed Wilms' tumour. This produced an actuarial estimate of 3% of offspring being affected by age 10 years, consistent with a larger risk than had been apparent from previous studies. [36] In contrast, no cancer was observed in 382 offspring of survivors of childhood leukaemia and non-Hodgkin's lymphoma - which under specific assumptions may provide an upper limit for the proportion of survivors who are likely to have hereditary disease. [37] The information on the occurrence of Wilms' tumour in the offspring of survivors was recently incorporated into a brief review of the current understanding of the biology of Wilms' tumour. [38] Recently we reported on the evidence for possible associations between childhood cancer and congenital abnormalities using information from the population-based National Register of Childhood Cancers. [39]

The paradigm which we have in mind to move from epidemiological observations to molecular genetics was summarised in the context of the epidemiological study of families with Li-Fraumeni Syndrome and the subsequent identification of germ line p53 mutations. [40]

PROPOSED STUDY METHODOLOGY – LIKELIHOOD OF SUCCESS

We have executed a Pilot Study to test all of the proposed study methods and this is discussed in detail in the accompanying document entitled "British Childhood Cancer Survivor Study - Pilot Study". In summary the overall response rate was almost 80% of eligible survivors returned a satisfactorily completed questionnaire. There was no evidence that response rate varied to any important extent by geographical location - which suggests that it is not unreasonable to regard the overall response rate as indicating what we might anticipate from the proposed national study. There was no evidence that questionnaire length affected the response rate to any important degree.

RESEARCH PLAN

Initially we shall need to approach the Office of National Statistics to obtain formal permission to extend the study to the whole of England and Wales. Similarly we shall need to obtain the permission of the Registrar General Office in Edinburgh to execute the study in Scotland. These permissions are required because the study population would be through the National Cancer Registration System.

As the study is national in coverage we shall need the permission of a Multi-Centre Research Ethics Committee. The principal investigator's appointment is now in the West Midlands - so this will be the appropriate Multi-Centre Research Ethics Committee to approach.

LOCAL RESEARCH ETHICS COMMITTEE PERMISSIONS

We shall be requesting the general practitioners to send out questionnaires directly to the patients and therefore it will be necessary to seek the permission of all Local Research Ethics Committees in England, Wales and Scotland.

NATIONAL HEALTH SERVICE CENTRAL REGISTER QUARTERLY UPDATES OF 'CURRENT POSTINGS'

The National Health Service Central Registers (Southport and Edinburgh) will be requested to provide quarterly lists of the current Health Authorities in which the survivors are registered with a general practitioner.

APPROACH EACH HEALTH AUTHORITY FOR GP NAMES AND ADDRESSES

With the information provided by the National Health Service Central Registers we shall approach the relevant Health Authorities to obtain the names and addresses of the general practitioner of survivors.

POSTAL SURVEYS FIELD WORK

We shall write to each general practitioner enclosing the following items:

1) The covering letter to the GP establishing the need for the study and asking for their co-operation;

2) The form which asks the GP to formally give their permission for their patient to be included in the study together with a reply paid envelope to the Study Co-ordinating Centre;

3) The suggested draft letter for the GP to send to their patient with the questionnaire inviting participation in the study;

4) The package to be mailed to the patient which will be contained in an envelope with first class postage paid. The GP will be asked to produce a covering letter, using the general practice letterhead, to accompany the package to the patient. The original of this letter should be placed within the package for the patient and the GP is asked to arrange for the package to be addressed to the patient and posted. It is requested that a copy of this letter should be mailed to the Study Co-ordinating Centre.

The package of documents posted to the patient by the general practitioner will contain:

1) The covering letter from the GP inviting the patient to participate in the study;

2) The covering letter from the Study Co-ordinating Centre;

3) The short explanatory leaflet for the patient;

4) The study questionnaire with individual patient details printed on the front;

5) A reply paid envelope for the patient to return the completed questionnaire to the Study Co-ordinating Centre.

The short explanatory leaflet for the patient addresses the common questions which survivors might have relating to the study. It is critically important that letters and enclosures emphasise that the outlook for most patients surviving at least five years after diagnosis of childhood cancer is good and that only a small number experience long term complications. However, it is also critically important that we understand why this small number are affected with a view to reducing the risk of such complications among patients treated in the future. We shall ask the general practitioner if the patient is currently on long term hospital follow up in relation to their childhood neoplasm, and if so, the name and address of the clinician concerned.

At the Study Co-ordinating Centre we shall provide 'free' 0800 helplines for patients who have difficulties or problems completing the questionnaire. We anticipate that most questions raised by the patients would be satisfactorily answered by staff at the Study Co-ordinating Centre. However, should the patient seek personal medical advice after completing the questionnaire then we would arrange for a medical doctor to be available.

An incentive to secure the co-operation of patients is the provision of a newsletter to those who participate. This newsletter will report progress of the study and important new findings for survivors.

It is possible that some survivors may be so impaired and dependent upon others, that it would be inappropriate to ask them to complete the form. In such circumstances, we are happy for a close relative or friend to complete the form with as much input from the survivor as is practical.

SURVIVORS AGED UNDER 16 YEARS

For survivors who are aged under 16 at time of contact we shall draft slightly amended letters and questionnaires and request that the general practitioner sends the questionnaire package to the parent or guardian who is also registered with the practice. When possible we shall request that it be sent to the survivor's mother.

OBTAINING TREATMENT DATA

For the 30% of survivors in the proposed cohort whose childhood cancer was treated within a clinical trial we could obtain the trial arm under which the patient was treated from the trial co-ordinators. This information is mostly stored on computers and therefore it would be comparatively inexpensive to obtain. Assuming that survivors received all cytotoxic drugs as specified in the trial protocol, and only those cytotoxic drugs, then the treatment information required for statistical analysis of the cohort study would thus be available. For the cohort study we would confine interest to drugs received and not consider doses of drugs. Previous research has shown that in these circumstances the assumption of treatment according to protocol will be overwhelmingly correct. [41] For patients entered into clinical trials it is known that treatment details, including doses of cytotoxic drugs, are likely to be kept centrally. In this way treatment histories for these patients should be protected against the highly variable policies of individual NHS Trusts in relation to the destruction of medical records. [33]

For the remaining 70% of survivors in the cohort not entered into a clinical trial it would be necessary to access the medical records which should be stored at the original treatment hospital(s). Although only individual cytotoxic drugs names would be needed for the cohort analysis, and not doses, it would be prudent to photocopy all medical records relating to chemotherapy. In the eventual nested case-control studies detailed doses of individual drugs would be required, and little extra effort is required to photocopy the relevant documents which need to be identified and read to be sure all drugs received have been recorded. This procedure would also protect against the potential destruction of notes by NHS Trusts in the time between the cohort study and subsequent nested case-control studies.

The anonymised detailed radiotherapy treatment records would be sent to Houston for classification of whether major organs of interest were directly irradiated. Dr Marilyn Stovall and her colleagues at the MD Anderson Cancer Center, Houston, Texas, are internationally acknowledged experts in providing radiation dosimetry for epidemiological investigations. Most studies of second cancer after childhood cancer which required radiation dosimetry involved collaboration with Dr Stovall - including all of our own such studies in Britain. Dr Stovall is already collaborating with the large treatment centre based study currently progressing in the USA which is addressing many of the objectives addressed by our proposed study. This US study was described on page 5 above. Employing Dr Stovall to do similar work for both the US and British studies would ensure that coding is carried out by an acknowledged expert and in comparable and consistent way.

STUDIES OF LONG-TERM SURVIVAL AND CAUSES OF DEATH AND SECOND CANCERS

The research methods to be used in these studies are similar to those which we have successfully used in the past, and described above. Therefore, we shall not describe these methods further here.

DATA MANAGEMENT

The research team who would be responsible for the proposed study has a history of successfully executing large epidemiological studies and therefore have the experience to establish satisfactory data management systems.

STATISTICAL ANALYSIS

Most of the analyses will involve standard statistical methods for the analysis of cohort and case-control studies. These methods have been described in detail in two monographs. [42, 43] Professor N E Day, who co-wrote both monographs, is Chairman of the Steering Committee for the proposed study. The research team who would execute the proposed study have previously analysed both cohort and case-control studies and therefore have developed a good practical knowledge of such statistical designs and their analysis. Cohort analyses would involve both internal and external comparisons. An example of an internal comparison would involve comparing the risk of serious cardiac adverse outcomes between survivors exposed to cardiotoxic anti-cancer drugs or radiotherapy which directly exposed the heart and survivors not exposed to such therapy. Proportional hazard (Cox) regression and Poisson regression are statistical methods which might be appropriate for such a comparison. External comparisons require some external source of data against which the survivor cohort may be compared. For example, comparing the rates of consultations with primary and secondary health care facilities between the survivor cohort and the general population using the General Household Survey as the external source of data. Observed and expected numbers of consultations could be compared using Poisson assumptions for statistical testing. For the application of case-control design and analysis see our previous work relating to second primary leukaemia and bone cancer. [16, 17]

A non-standard aspect of statistical analysis arises in the analysis of outcomes of pregnancy and health of offspring. Through the intra-family correlations the assumption observations being independent is violated. Methods which accommodate this intra-family correlation will be required.[44]

Analysis of the data concerning the familial occurrence of cancer and related conditions may require specialized statistical methods, for example segregation analysis.

EXTENT OF RESEARCH PROTOCOL

This research protocol is almost exclusively concerned with analyses of the cohort study; nested case-control studies will be the subject of further grant applications with one exception. The exception concerns already planned case-control studies of second primary neoplasms. Specifically we plan two case-control studies: one of second primary soft tissue sarcomas; the other of second primary tumours of the central nervous system. We have budgeted for the costs associated with obtaining pathological blocks of tissue relating to the two neoplasms developing in each case. The reason for obtaining these blocks as soon as practicable is that increasingly, since the introduction of NHS Trusts, historical pathological sections and blocks are being destroyed. Particularly when patients have died. We have not budgeted for the biological studies to be based on these tissue samples. These biological aspects of the study of second cancers would be the subject of separate grant applications and ethical approvals.

A preliminary to any nested case-control study would likely be confirmation of the adverse outcomes concerned - for example cardiac events. We have not budgeted for such confirmation as this would more appropriately form part of a grant application for each case-control study concerned.

RELATED STUDIES ALREADY PLANNED - BUT SUBJECT OF SEPARATE GRANT APPLICATIONS

1) Biological studies of the genetic determinants of second cancers. A valuable source of biological material would be pathological blocks relating to cancers diagnosed. We would investigate the frequency of germ line mutations for evidence of genetic susceptibility. Studying the patterns of somatic alterations in tumour tissue, in the relation to types of treatment received for the original childhood cancer, may help clarify the aetiology of second cancers.

2) Case-control studies of adverse health outcomes, other than second cancers, among survivors for which there is evidence from the cohort study of important variation by, for example, type of treatment, year of treatment, age at treatment or diagnosis. *A priori* it seems likely that serious cardiac outcomes and pulmonary outcomes will each be the subject of such a case-control study.

OTHER RELATED STUDIES BEING CONSIDERED

1)   Blood or buccal smears might be obtained from all survivors within the cohort, or sub-groups considered to be at particular risk of specific adverse health outcomes, with a view to prospectively investigating the role of genetic influences on development of adverse health outcomes.

2)   Study the impact of particular intervention strategies with a view to prevention if possible, or early diagnosis and improved long-term prognosis in high risk sub-groups identified from the cohort study.

3)   Study the potential impact of growth hormone on recurrence and development of second cancer.

4)   Collaborate in the development of more refined measures of self-assessed health-related quality of life.

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APPENDIX A

CHARACTERISTICS OF THE COHORT POPULATION

Diagnosis

Leukaemia	4841	(27%)
Hodgkin's disease	1319	(7%)
Non-Hodgkin lymphoma	962	(5%)
CNS tumours	4144	(23%)
Neuroblastoma	766	(4%)
Retinoblastoma	1197	(7%)
Wilms' tumour	1478	(8%)
Bone Sarcoma	647	(4%)
Soft tissue sarcoma	1204	(7%)
Other	1448	(8%)
	18006	(100%)

Decade at treatment

1940's	104	(1%)
1950's	1024	(6%)
1960's	2641	(15%)
1970's	5415	(30%)
1980's	7101	(39%)
1990's	1721	(10%)

Age at contact (years)

At least 40	2186	(12%)
30-39	3967	(22%)
20-29	6067	(34%)
16-19	2464	(14%)
5-15	3313	(18%)

Sex

Male	9906	(55%)
Female	8100	(45%)